REMARKS

Claims 1 to 13, 20, 22, and 24 to 27 are pending in the application. Claim 22 stands withdrawn and claims 14 to 19, 21, and 23 were previously canceled. New claims 25 to 27 have been added. The amendments are supported throughout the specification and by the claims as originally filed, *e.g.*, page 12, lines 10-14; and claim 1. The amendments add no new matter to the application.

Withdrawn Rejections

Applicant notes with appreciation the withdrawal of the prior rejections made under 35 U.S.C. §§ 102(b) and 103(a). The claims are now rejected, however, on the basis of reformulated or new anticipation and obviousness rejections. In view of the remarks that follow, the Office is asked to reconsider and withdraw the present rejections.

Rejections under 35 U.S.C. § 102(a)

Claims 1 to 3, 6 to 9, 13, 20, and 24 were rejected as allegedly anticipated by Ribeiro *et al.* (*Lancet* 360:461-462, 2002; hereinafter "Ribeiro"). The Office alleges that Ribeiro "teaches a method of predicting whether a patient has cardiomyopathy comprising analyzing the BNP levels of Chagas' disease patients" (*see*, the Office Action at page 5).

Applicant respectfully traverses. Ribeiro states that "[p]atients with Chagas' disease have high plasma concentrations of BNP in association with impaired left ventricular function" (*see,* page 462, col. 1, lines 16-18). However, Ribeiro does not describe cardiomyopathy or myocarditis, or associate an elevated BNP level in Chagas disease with cardiomyopathy or myocarditis, as presently claimed. Therefore, it appears that the Office's position is that left ventricular dysfunction (LVD) is equivalent to cardiomyopathy or myocarditis. Applicant respectfully submits that this is an incorrect reading of Ribeiro. Skilled practitioners would clearly appreciate that LVD is wholly distinct from cardiomyopathy and myocarditis. LVD, with subsequent congestive heart failure, constitutes the final stage for a host of cardiac disorders, including cardiomyopathy and myocarditis, and it would be incorrect to equate LVD with either

cardiomyopathy or myocarditis since they are neither equivalent nor interchangeable. A patient having cardiomyopathy or myocarditis does not necessarily suffer from LVD and *vice versa.* This position is supported by the studies of Lima *et al.* (*Circulation* 73:172-179, 1986; "Absence of left ventricular dysfunction during acute chagasic myocarditis in the rhesus monkey," a copy provided as Exhibit A; hereinafter "Lima"). Lima teaches that

> "acute chagasic myocarditis may be severe after *T. cruzi* infection, yet cause no impairment in resting left ventricular function despite intense intracellular *T. cruzi* invasion" (*see*, Lima at Abstract, page 172; emphasis added); and
>
> "[a]utopsy in the approximately 10% of patients who die during the acute stage of Chagas' disease frequently reveals myocarditis that in some cases is far more severe than previously suspected on the basis of clinical data, x-rays, and/or electrocardiograms. These discrepancies have been attributed to incomplete assessment of left ventricular function. Our data, however, support another explanation: Left ventricular dysfunction is not an early consequence of severe myocardial involvement by *T. cruzi*" (*see,* Lima at page 175, left column, line 3, to page 176, left column, line 2; emphasis added).

Unlike Ribeiro, applicant has shown that an increase in the level of BNP, or both BNP and ANF, in a patient suffering from an infection correlates with a diagnosis of cardiomyopathy and/or myocarditis even before the disease has progressed far enough for the patient to exhibit clinical signs of cardiomyopathy, myocarditis, or LVD. The claimed methods can be used to predict cardiomyopathy, myocarditis, or both, resulting from an infection, which is clearly beneficial because it allows for therapeutic intervention and monitoring early in the disease process and before cardiomyopathy, myocarditis, or LVD has developed. To the contrary, Ribeiro assessed patients in the chronic phase of Chagas disease and consequent to heart dysfunction, as measured by left ventricular ejection fraction (LVEF). Indeed, Ribeiro discloses that significantly higher levels of BNP are correlated with patients exhibiting reduced LVEF (*see*, Ribeiro at page 462, left column, ¶ 1), but fails to show that an increase in the level of BNP, or both BNP and ANF in a sample, compared to the level of BNP, or both BNP and ANF in a control group, is predictive of whether a patient is susceptible to cardiomyopathy, myocarditis, or both, resulting from an infection. Accordingly, the rejection should be withdrawn.

Rejections under 35 U.S.C. § 103(a)

1. Claims 1 to 4, 8, 11 to 13, 20, and 24 were rejected as allegedly obvious over Ribeiro in view of Arad *et al.* (*Cardiology* 87:12-17, 1996; hereinafter "Arad") and Totsune *et al.* (*Regul Pept* 63:141-147, 1996; hereinafter "Totsune"). In working to support the rejection, the Office refers to the disclosure of Ribeiro as it allegedly applies to claims 1 to 3, 6 to 9, 13, 20, and 24, but concedes Ribeiro does not describe atrial natriuretic peptides (ANP), which the Examiner contends can be found in Arad, or teach a body fluid comprising urine, which the Examiner contends can be found in Totsune.

Applicant respectfully traverses. As explained above, Ribeiro associates elevated BNP levels with LVD. Lima establishes that LVD is not an early consequence of severe myocardial involvement by *T. cruzi*, and thus skilled practitioners would not equate LVD in Chagas disease with cardiomyopathy or myocarditis, resulting from an infection. Arad and Totsune do not cure this deficiency for at least the following reasons.

Arad studied heart function and heart failure (a mechanical concept) and does not even mention an infection of any kind. Arad states that "[i]n the current study we evaluated the hormone levels in patients with ischemic heart disease manifested predominantly by angina pectoris with or without overt heart failure" (*see*, page 16, col. 2, lines 3-6; emphasis added). In contrast, the present claims recite methods of predicting whether cardiomyopathy, myocarditis, or both, will arise as a result of an infection in a human patient. As shown by applicant, elevated levels of BNP or BNP and ANF are measured after a patient suffers an infection and these levels correlate with the occurrence of cardiomyopathy and/or myocarditis. Arad does not disclose that one should assess BNP, or BNP and ANF, to predict whether cardiomyopathy or myocarditis will arise as a result of an infection.

With respect to the feature "wherein the body fluid comprises urine," the claimed methods also cannot be considered obvious based on the combined teachings of Ribeiro, Arad, and Totsune because nothing in Totsune teaches or suggests that BNP, or BNP and ANF, can be used as predictive indicators of cardiomyopathy, myocarditis, or both, resulting from an infection. As claim 1 is non-obvious, all of its dependents, including claims 2 to 4, 8, 11 to 13,

20, and 24 are also non-obvious for at least the same reasons. Accordingly, applicant requests that the rejection be withdrawn.

What must be obvious is the claimed invention as a whole. "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious" (MPEP at 2141.02, emphasis in original, citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)). Thus, the determination is not whether it would have been obvious to analyze urine, but whether it would have been obvious to analyze BNP, or BNP and ANF, in urine as a predictive indicator for cardiomyopathy, myocarditis, or both, resulting from an infection.

Accordingly, no combination of Ribeiro, Arad, and Totsune renders the subject matter of claims 1 to 4, 8, 11 to 13, 20, and 24, or new claims 25 to 27 obvious and the rejection should be withdrawn.

2. Claims 1 to 3, 5 to 13, and 20 were rejected as allegedly obvious over Ribeiro in view of Arad and Kaneko *et al.* (*Brain Res* 612:104-109, 1993 (Abstract only); hereinafter "Kaneko"). In an attempt to support the rejection, the Office refers to the disclosures of Ribeiro and Arad as applied to claims 1 to 4, 8, 11 to 13, 20, and 24 above. In addition, the Office asserts that it would be obvious to substitute the body fluid sample taught in Ribeiro, *i.e.,* blood, or Arad, *i.e.,* plasma, for the body fluid sample taught in Kaneko, *i.e.*, cerebrospinal fluid. Applicant respectfully disagrees.

The distinguishing features of claim 1 over Ribeiro and Arad are discussed in detail above. Kaneko does not cure the deficiencies of Ribeiro and Arad. Kaneko is combined with Ribeiro and Arad by the Office in an attempt to provide the element recited in claim 5, *i.e.*, cerebrospinal fluid as the body fluid. Arad and Kaneko do not remedy the other shortcomings of Ribeiro. In particular, Arad and Kaneko do not teach or suggest that an increased BNP level is a useful marker of infection-related cardiomyopathy or myocarditis. Regardless of whether or not multiple tests can be performed on multiple samples collected at

different times, or whether BNP and ANF can be detected in cerebrospinal fluid, the present methods are non-obvious because, *inter alia*, nothing in the combined teachings of Ribeiro, Arad, and Kaneko suggest that BNP, or BNP and ANF, can be used as predictive indicators of cardiomyopathy or myocarditis in human patients who have an infection. What must be obvious is the claimed invention as a whole. "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious" (MPEP at 2141.02, emphasis in original, citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)). Thus, the determination is not whether it would have been obvious to perform multiple tests on multiple samples collected at different times, but whether it would have been obvious to do so as a predictive indicator for cardiomyopathies and myocarditis that arise as a result of an infection. Similarly, the determination is not whether it would have been obvious to analyze cerebrospinal fluid, but whether it would have been obvious to analyze BNP, or BNP and ANF, in cerebrospinal fluid as a predictive indicator as required by the claims. As claim 1 is non-obvious, all of its dependents, including claims 2, 3, 5 to 13, and 20 are also non-obvious for at least the same reasons. Accordingly, the rejection should be withdrawn.

3. Claims 1 to 3, 6 to 13, and 24 were rejected as allegedly unpatentable over Ribeiro in view of Arad and Mischak *et al.* (WO 97/32900; hereinafter "Mischak"). The Office refers to the disclosures of Ribeiro and Arad as applied to claims 1 to 4, 8, 11 to 13, 20, and 24 above and concedes that Ribeiro and Arad do not teach the element of "the at least one antibody comprises a monoclonal antibody" (*see,* the Office Action at page 16). Mischak is combined with Ribeiro and Arad by the Office in an attempt to arrive at claim 10. Applicant respectfully traverses.

The distinguishing features of claim 1 over Ribeiro and Arad are discussed in detail above. Mischak does not cure the deficiencies of Ribeiro and Arad. In particular, Mischak does not teach that an increased BNP level is a useful marker of infection-related cardiomyopathy or myocarditis. Mischak describes only reagents and assays for the quantification of human BNP in plasma and serum, including monoclonal antibodies. Mischak does not teach or suggest that an

increase in the level of BNP, or both BNP and ANF in a sample from a patient, compared to the level of BNP, or both BNP and ANF in a control group, indicates that cardiomyopathy, myocarditis, or both cardiomyopathy and myocarditis will arise as a result of an infection in the patient. Mischak fails to overcome the deficiencies of Ribeiro and Arad, and therefore does not render obvious claim 10. Accordingly, applicant respectfully requests the rejection be reconsidered and withdrawn.

Applicant respectfully submits that the Office has not established a *prima facie* case of obviousness against the presently claimed methods. No combination of Ribeiro, Arad, Totsune, Kaneko, and Mischak, teach or suggest every element of the claims. Further, skilled practitioners would not have been motivated by these references, or anything else in the art, to modify the method described in Arad in an attempt to arrive at applicant's claimed methods. Even if a skilled practitioner were to combine these references, the claimed methods still would not have been obtained because they do not teach or suggest all recited elements. Applicant therefore respectfully requests that these rejections be reconsidered and withdrawn.

CONCLUSION

Applicant submits that the pending claims are allowable and request early and favorable action thereon. Applicant does not concede any positions of the Office that are not expressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

The Petition for Three-Month Extension of Time fee ($1110) is being paid on the electronic filing system by way of deposit account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14703-0002001.

Respectfully submitted,

Date: 11/28/10

Todd E. Garcia, Ph.D.
Reg. No. 54,112

Fish & Richardson P.C.
Customer Number 26161
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

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